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278. (New) A method for evolving a polypeptide having an altered immunogenicity or stability, the polypeptide being encoded by a DNA substrate molecule, the method comprising:

- (a) providing a library of variants of the DNA substrate molecule;
- (b) transforming the variants of the DNA substrate molecule of (a) into host cells;
- (c) expressing the variants of (b) to provide polypeptide expression products and derivatizing the polypeptide expression products with a moiety capable of altering immunogenicity or stability; and
- (d) screening or selecting from the derivatized polypeptide expression products of (c) to identify at least one evolved polypeptide having an altered immunogenicity or stability relative to the polypeptide encoded by the DNA substrate molecule that is derivatized with the moiety.

279. (New) The method of claim 278, wherein the variants of (a) are generated by one or more of: recursive sequence recombination, PCR mutagenesis, cassette mutagenesis, oligonucleotide-directed mutagenesis, site-directed mutagenesis, doped oligo mutagenesis, chemical mutagenesis, or propagation of the DNA substrate molecule through bacterial mutator strains.

280. The method of claim 278, further comprising:

- (e) recovering at least one evolved DNA substrate molecule encoding the at least one evolved polypeptide of (d); and
- (f) subjecting the at least one evolved DNA substrate molecule of (e) to mutagenesis to generate mutagenized products.

281. (New) The method of claim 280, wherein the mutagenesis comprises one or more of: recursive sequence recombination, PCR mutagenesis, cassette mutagenesis, oligonucleotide-directed mutagenesis, site-directed mutagenesis, doped oligo mutagenesis, chemical mutagenesis, or propagation of the DNA substrate molecule through bacterial mutator strains.

282. (New) The method of claim 278, wherein the moiety capable of altering immunogenicity or stability is a polymer.

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283. (New) The method of claim 278, wherein the at least one evolved polypeptide has improved stability.

284. (New) The method of claim 278, wherein the at least one evolved polypeptide has reduced immunogenicity.

285. (New) The method of claim 278, wherein (c) comprises expressing the variants of (b) to provide polypeptide expression products, purifying the polypeptide expression products, and derivatizing the polypeptide expression products with a moiety capable of altering immunogenicity and/or stability.

286. (New) The method of claim 278, wherein the derivatized polypeptide expression products of (c) are derivatized post-translationally.

287. (New) The method of claim 278, wherein the at least one evolved polypeptide has reduced immunogenicity and improved stability.

288. (New) The method of claim 278, wherein the host cells comprise eukaryotic cells.

289. (New) The method of claim 280, wherein the mutagenized products are used as the library of variants in a repeated (a).

290. (New) A method for evolving a polypeptide having an altered immunogenicity, the polypeptide being encoded by a DNA substrate molecule, the method comprising:

- (a) providing a library of variants of the DNA substrate molecule;
- (b) transforming the variants of the DNA substrate molecule of (a) into host cells;
- (c) expressing the variants of (b) to provide polypeptide expression products;

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(d) screening or selecting from the polypeptide expression products of (c) to identify an evolved polypeptide having an altered immunogenicity relative to the polypeptide encoded by the DNA substrate molecule that is derivatized with the moiety;

(e) recovering an evolved DNA substrate molecule that encodes the evolved polypeptide of (d); and

(f) expressing the evolved DNA substrate molecule, thereby providing the evolved polypeptide having altered immunogenicity.

291. (New) The method of claim 290, wherein the altered immunogenicity comprises reduced immunogenicity.

292. (New) The method of claim 290, wherein the host cells comprise eukaryotic cells.

293. (New) A method of identifying a polypeptide having an altered immunogenicity or stability, the method comprising:

(a) providing a mixture of nucleic acid subsequences of two or more parental polynucleotides, wherein each parental polynucleotide differs from at least one other parental polynucleotide in at least one nucleotide and encodes at least one polypeptide or fragment thereof;

(b) extending one or more of the nucleic acid subsequences with at least one polymerase to produce one or more recombined polynucleotides that each encode one or more polypeptide variants;

(c) expressing the one or more recombined polynucleotides to provide the one or more polypeptide variants and derivatizing the one or more polypeptide variants with a moiety capable of altering immunogenicity or stability;

(d) screening or selecting the one or more polypeptide variants to identify at least one polypeptide variant having altered immunogenicity or stability compared to polypeptides derivatized with the moiety, which polypeptides are encoded by the two or more parental polynucleotides;

(e) recovering at least one recombined polynucleotide encoding the at least one cytokine variant identified in step (d); and

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(f) repeating (a)-(d) using the at least one recombined polynucleotide recovered in step (e) as at least one of the two or more parental polynucleotides of a repeated step (a).

294. (New) The method of claim 293, wherein the host cells comprise eukaryotic cells.

295. (New) A method for evolving a polypeptide having an altered immunogenicity or stability, the polypeptide being encoded by a DNA substrate molecule, the method comprising:

- (a) providing a library of variants of the DNA substrate molecule;
- (b) transforming the variants of the DNA substrate molecule of (a) into host cells;
- (c) expressing the variants of (b) to provide polypeptide expression products and derivatizing the polypeptide expression products with a moiety capable of altering immunogenicity or stability; and
- (d) screening or selecting from the derivatized polypeptide expression products of (c) to identify at least one evolved polypeptide having an altered affinity for a receptor or a ligand relative to the polypeptide encoded by the DNA substrate molecule which polypeptide is derivatized with the moiety.

296. (New) The method of claim 295, wherein the host cells comprise eukaryotic cells.

For the Examiner's convenience, a markup copy of the claims is included herewith as Appendix A and a complete claim set of the currently pending claims is also submitted herewith as Appendix B. These amendments are made without prejudice to subsequent renewal, including in a related divisional or continuation application, and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

REMARKS

New claims 278-296 are presently pending. Claims 274-277 have been canceled herein without prejudice to subsequent renewal. Claims 1-273 were previously canceled without

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prejudice to subsequent renewal. Applicants specifically reserve the right to pursue claims directed to all or any portion of the subject matter that was canceled by this Amendment or the previous Amendment in one or more continuation and/or divisional applications.

No new matter is introduced by new claims 278-296. Support for the subject matter of the new claims is found throughout the specification and claims as originally filed and, for example, on pages 69-71 of the specification. Specific support for some of the subject matter of the new claims is as follows: Support for derivatizing polypeptides with chemical moiety is found at page 69, line 30 to page 70, line 6. Support for reduced immunogenicity is found, e.g., at page 69, line 30 to page 70, line 6. Support for reduced immunogenicity is found, e.g., at page 69, line 30 to page 70, line 6. Support for altered affinity for a receptor or ligand is found, e.g., at page 69, lines 269, line 30 to page 70, line 6. Support for increased stability is found, e.g., at page 70, lines 26-32. Support for screening or selecting polypeptides for desired properties is found, e.g., at page 31, lines 12 and 13. Support for eukaryotic cells as host cells is found, e.g., at page 14, lines 34-37.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,



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